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CHAPTER 223

SEX HORMONES AND HUMAN CARCINOGENESIS: EPIDEMIOLOGY

ROBERT N. HOOVER

Because of the central role that the hormonal milieu plays in various carcinogenic processes, clinical endocrinologists must be aware of malignancies to which their patients may be predisposed, either because of the nature of their illness or because of the nature of the hormonal therapy being instituted.

CARCINOGENESIS AND ENDOGENOUS SEX HORMONE STATUS

Endogenous hormone status has long been thought to be an important factor in the etiology of a number of human malignancies. This belief has been based on animal carcinogenesis studies (see Chap. 222), the responsiveness of a number of tumors to hormonal manipulation (see Chaps. 224 and 225), the relationship of risk of certain tumors to a variety of reproductive and other factors thought to influence hormonal status, and the simple fact that some organs depend on hormonal status for their normal function.[1] Speculation about a causal role for hor-

mones has focused on malignancies of the female breast and the reproductive tract. Some evidence for hormonal carcinogenesis has been observed for a variety of other tumors, however, including prostate, liver, testis, thyroid, and gallbladder cancers, and malignant melanoma. Despite these long-standing suspicions, little success has been achieved in identifying the specific hormonal factors that might be responsible for these tumors, with the possible exception of endometrial cancer.

CARCINOGENESIS AND EXOGENOUS SEX HORMONE THERAPY

Within the last 50 years, a new element in the area of hormonal influences on cancer risks has been added, that of exogenous sex hormone exposure. Pharmacologic levels of estrogens, progestins, androgens, and pituitary trophic hormones, alone or in combination, have been administered to large segments of the population for various reasons. These large-scale "natural experiments" have provided more specific insights into the relationship between hormonal factors and several different malignancies.[2] Moreover, enthusiasm has grown for the widespread treatment of relatively healthy segments of the population (e.g., women receiving oral contraceptive agents or menopausal replacement therapy). Considerable interest has arisen in the use of estrogens for postmenopausal prevention of osteoporosis and osteoporotic fractures[3] (see Chaps. 64 and 100). Some evidence supports the long-suspected potential of menopausal estrogens to prevent clinical coronary heart disease.[4] In addition, within the general population, a substantial increase has been seen in the use of dietary supplements, many of which have significant hormonal activity (e.g., androstenedione, melatonin). Because of this enthusiasm on the part of physicians and the public, appropriate evaluations of the carcinogenic consequences of these exposures has become important to public health, as well as to understanding the biology of the tumors involved.

ENDOMETRIAL CANCER

ENDOGENOUS FACTORS IN ENDOMETRIAL CANCER

The cancer for which the evidence for both an endogenous and an exogenous hormonal cause is best established is endometrial cancer.

Various factors related to endogenous hormone production have been associated with endometrial cancer.[5] Medical conditions related to increased risk include functional (estrogen-secreting) ovarian tumors, the polycystic ovary syndrome, diabetes mellitus, and hypertension. Reproductive factors, including nulliparity and a late natural menopause, also have consistently been found to be related to increased risk. Some dietary factors also seem to influence risk. Obesity is a risk factor and a vegetarian diet is a possible protective factor.[6] Age, a determinant of levels of most endogenous hormones, also influences endometrial cancer risk in a unique manner. Endometrial cancer rates are extremely low in women younger than 45 years of age, rise precipitously among women in their late 40s and throughout their 50s (much more dramatically than for other tumors), and then decline in women approximately age 60 and older (Fig. 223-1).

EXOGENOUS SEX HORMONES AND ENDOMETRIAL CANCER

Exposure to exogenous hormones also has been linked to endometrial cancer.[5]

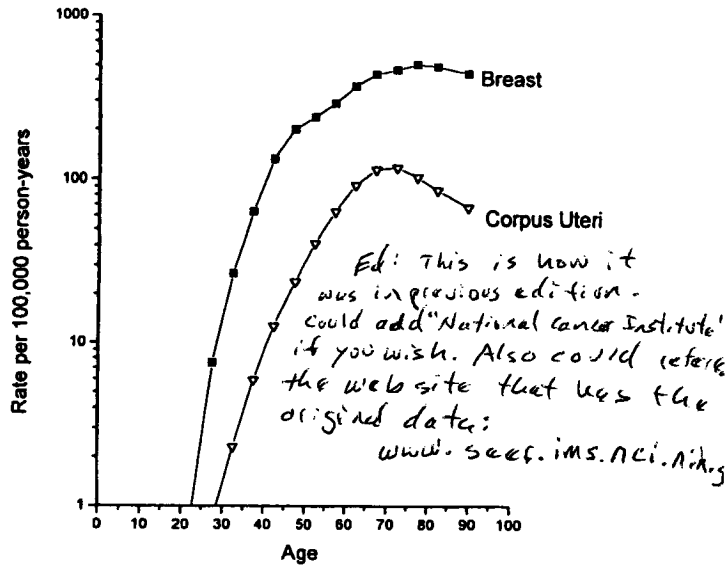

FIGURE 223-1. Age-specific incidence rates for breast and uterine corpus cancers among white women during 1986 through 1990. (Data from the Surveillance, Epidemiology and End Results Program.) [AUQ 4]

ESTROGENS AND ENDOMETRIAL CANCER

Estrogen-replacement therapy of 2 years or longer for menopausal women is associated with an excess *relative risk* of endometrial cancer. Table 223-1 shows estimated relative risks (i.e., the risk of the disease among those exposed to estrogen therapy compared with the risk among those not exposed).[7-14] The relative risk among users compared with nonusers ranges from two-fold to eight-fold. It increases even further with long duration of use and with high average daily doses. Thus far, every type of estrogen that has been investigated has shown this relationship, including conjugated equine estrogens, ethinyl estradiol, and diethylstilbestrol (DES). The highest risk occurs among current users. The risk declines with each year after cessation of use, although apparently some residual excess risk is present even 10 years after cessation. The risk is highest for early-stage malignancies, but a two-fold to three-fold excess risk is seen for the advanced stages of disease as well.

EFFECT OF ESTROGEN AND PROGESTERONE IN SEQUENCE

A profound trend has been seen away from unopposed estrogen treatment of menopausal symptoms and toward treatment with

TABLE 223-1.
Relative Risks* of Endometrial Cancer Associated with Menopausal Estrogen Use from Selected Case-Control Studies

Reference	Source of Controls	Overall RR	RR among Long-Term Users†
Ziel and Finkle[7]	Health plan	7.6	13.9
Mack et al.[8]	Retirement community	5.6	8.8
Gray[9]	Private practice	3.1	11.6
Pike et al.[10]	Community	2.1	24.2
Green et al.[11]	General population	3.7	16.3
Hulka et al.[12]	Gynecology patients	1.8	4.1
Shapiro et al.[13]	Hospital patients	3.9	6.0
Brinton et al.[14]	Community	3.0	6.0

RR, relative risk.
*Risk of cancer relative to a risk of 1.0 for women who never used menopausal estrogens.
†Definition of *long term* varied from ≥5 to ≥15 years.

through circulating estrogen levels—obesity—was unchanged when controlled for estrogen levels. Thus, although the model is attractive, additional work is needed to determine its place in the understanding of endometrial carcinogenesis. Even so, the model does suggest several promising lines of future clinical, epidemiologic, and laboratory research.

Perhaps most important to an understanding of carcinogenesis is the clarification of the precise mechanism by which circulating estrogens produce endometrial cancer. Several possibilities have been proposed: that estrogens are complete carcinogens themselves; that they promote initiated cells; or that they simply stimulate growth and, thereby, offer a greater opportunity for abnormal cells to arise or for carcinogens to act on vulnerable genetic material. The epidemiologic evidence strongly favors the argument that estrogens act at a relatively late stage in the process of carcinogenesis. If estrogens are promoters, however, no initiators of the process are readily apparent.

BREAST CANCER

The hormonal etiology of breast cancer is well accepted, but no accepted unified model for the mechanism exists. Several hormonal hypotheses have been suggested, but extensive supporting data are lacking.

ENDOGENOUS FACTORS IN BREAST CANCER

The importance of the ovary in breast cancer etiology is demonstrated by its relationship to a number of breast cancer risk factors.[28] Earlier age at menarche is associated with high risk of breast cancer. Similarly, later age at natural menopause also is associated with elevated risks. Surgical removal of the ovaries before natural menopause reduces risk of breast cancer, and the earlier the operation, the lower the risk. The shape of the age-incidence curve for this disease (see Fig. 223-1) has been interpreted as showing that the onset of ovarian activity early in life determines the slope of the curve, and that a reduction in this ovarian factor around the time of menopause is responsible for the change in the slope of the curve at ~50 years of age.

Other risk factors for breast cancer also have been well established. *A history of breast cancer in a first-degree relative elevates a woman's risk of contracting breast cancer two-fold to five-fold.* Historical observations of a protection against breast cancer associated with an increase in parity were found to reflect the influence of the age at first birth. A woman who has her first child after the age of 30 years has approximately two-fold to three-fold the risk of breast cancer of a woman who had her first child when younger than 18 years of age. Nulliparous women have approximately the same risk as those women who had their first child at 30 years of age, whereas women who have a first birth after this age actually experience a greater risk than do nulliparous women. Investigations[29] have implied that increased parity may indeed diminish the risk of breast cancer, even when controlled for age at first birth. Benign breast disease, particularly that containing hyperplastic or dysplastic elements, places a woman at a two-fold to five-fold excess risk of subsequent breast cancer.[30] Body size also relates to breast cancer risk. Height or frame size is positively associated with risk. Obesity, or an increasing body mass index, is associated with an increased breast cancer risk among menopausal women, and a decreased breast cancer risk among premenopausal women.[31] Evidence implies that increased weight contributes as a risk factor only in the years immediately before diagnosis, which suggests that the mechanism involved operates very late in the process of breast carcinogenesis.[32]

INFLUENCE OF DIET

Diet, particularly a diet high in caloric and/or fat intake, is strongly suspected of playing a role, because of worldwide differences in breast cancer rates. Asian populations have rates five-fold to six-fold lower than those seen in the United States and Western Europe. Migrants from Japan and China to the United States experience risks that rise toward the levels of whites over the course of two generations of residence within the United States. Whereas some direct support[33] for these dietary hypotheses has been proposed, a number of studies[34–37] have found no relationship, and the entire area remains controversial.

HYPOTHESES FOR THE HORMONAL CAUSATION OF BREAST CANCER

A unifying hormonal hypothesis for breast cancer is frequently speculated to be possible, because even the nonovarian risk factors actually may operate through a hormonal mechanism. Perhaps the simplest of these models[38] is that breast cancer risk reflects total lifetime, or perhaps total early life, dose of estrogens. Related to this is the unopposed-estrogen hypothesis,[39] which also assumes that estrogens are the important risk factor but emphasizes the relative protective role of progesterone. Other hypotheses have suggested that, rather than total estrogens, specific individual estrogens and/or their metabolites may be the operative agents, in keeping with their differing carcinogenic or mitogenic potencies.[40,41] Another hypothesis[42] holds that the proportion of free versus protein-bound estrogen determines a woman's breast cancer and endometrial cancer risk. Speculation has also arisen that progesterone might actually be hazardous rather than protective because, contrary to its action on the endometrium, it seems to act as a mitogen within the breast ductal epithelium. Historically, androgens had been viewed as protective through their antiestrogenic action. Subsequently, however, laboratory and epidemiologic studies have suggested the opposite, perhaps due to the roles of androgens as precursors of estrogen synthesis.[43] Finally, pituitary hormones and prolactin in particular have been suggested as being primarily involved in breast carcinogenesis.[44,45]

Confirmation for these hypotheses has been sought by measuring levels of various hormones: first, in breast cancer patients and controls either at the time of diagnosis or at some time before; and second, in women with different levels of known risk factors, to determine whether the risk factors operate through specific hormones. In general, these studies have tended to find higher estrogen levels in women with breast cancer than in controls, at least among menopausal women. The level of difference has been highly variable, however, and often restricted to subgroups of women that also differ from study to study. Interestingly, subsequent studies have also noted elevations of several different adrenal androgens in women with breast cancer.[43] [AU: Q1] Studies of hormonal profiles related to various breast cancer risk factors have been few and have produced little in terms of consistent patterns. As a result, although they add to the evidence that estrogens are related to breast cancer risk, taken together, all of these laboratory-epidemiologic studies fail to rule out any of the proposed models of endogenous hormone effects as a partial explanation, and they also fail to support any one model as the unified explanation, perhaps because the women are being tested at ages other than those critical for breast cancer risk modification. Or, perhaps, the premise of a unifying hypothesis is incorrect.

Thus, although the evidence that breast cancer is a tumor of hormonal etiology is overwhelming, all of the specific endogenous hormones involved and their relative roles remain elusive.

substantial impact on subsequent breast cancer risk. Whether this effect would be hazardous or beneficial was hotly debated. Most studies, however, have found essentially no overall relationship between the use of oral contraceptives and the risk of breast cancer.

The large number of studies of this issue and the large size of some of these studies have allowed assessments of risk according to different patterns of use and in multiple subgroups. Accordingly, a variety of questions were raised. The inconsistencies across studies prompted a large pooled analysis similar to that described above for HRT.[53] The considerable power resulting from the inclusion of more than 53,000 cases yielded consistent findings that were similar in many respects to those seen for HRT. *Breast cancer risk is increased in oral contraceptive users, but only among relatively recent users and to a lesser extent than for HRT.* Specifically, compared with those who had never used such contraceptives, the risks were 24% higher for current users, 16% higher for those who stopped use in the 5 years before diagnosis, and 7% higher for those who stopped 5 to 9 years earlier. These findings were remarkably consistent across various levels of other breast cancer risk factors. Also, as with the findings for HRT, these risks were more pronounced for less clinically advanced disease.

TAMOXIFEN AND BREAST CANCER

An ancillary observation made during the conduct of clinical trials on the effect of tamoxifen treatment for breast cancer was the dramatic reduction in the risk of development of a new breast cancer in the contralateral breast in the tamoxifen-treated groups. This led to the development of several randomized clinical trials of tamoxifen as a preventive agent in women at high risk of breast cancer but without a prior history of the disease. The largest such trial found a 49% reduction in the incidence of breast cancer in the tamoxifen group, which came entirely from a 69% reduction in estrogen receptor–positive tumors.[25] Significant side effects occurred. In addition to the increase in risk of endometrial cancer noted above, the rates of stroke, pulmonary embolism, and deep-vein thrombosis also increased in the tamoxifen-treated group. The results of this trial have spurred enthusiasm for tests of the efficacy of related compounds that might carry a smaller risk of serious side effects.

FUTURE IMPERATIVES

Clearly, the long-term consequences of oral contraceptive use on breast cancer risk will remain a research subject for many years. Only now are substantial numbers of women who used oral contraceptives for 5 or more years early in their reproductive lives entering the ages of high breast cancer risk. Thus, the final conclusion on long-term sequelae of oral contraceptive use must be postponed.

The current enthusiasm for cyclic estrogen-progestogen treatment of menopausal symptoms offers the opportunity to investigate an exposure of particular relevance to a number of the etiologic theories concerning the hormonal basis of breast cancer. Continued development of such studies seems to warrant a high priority, both on this basis and because of the sudden onset of treatment of a large population of healthy women with this currently understudied drug combination therapy.

In addition, because of the lack of practical opportunities to prevent breast cancer by altering known risk factors, enthusiasm has grown for the use of potentially chemopreventive drugs, most of which have a hormonal action. The tamoxifen experience continues, but other even more imaginative regimens have been suggested.[54] As for tamoxifen therapy, such treatments are likely to have unanticipated consequences, as well as, one hopes, the desired result. Thus, close study of such treatment groups may provide unique insights into hormonal carcinogenesis in human populations.

OVARIAN CANCER

Much less is known about risk factors for ovarian cancer than about risk factors for cancers of the endometrium and breast. Until the late 1970s, the issue was little studied, but several extensive epidemiologic investigations have been undertaken.

ENDOGENOUS FACTORS IN OVARIAN CANCER

Only a few risk factors for ovarian cancer have been identified in these investigations, and they account for only a small proportion of the disease. However, the few factors consistently identified clearly imply a hormonal cause for this malignancy.[5] First of all, parity is protective, with the risk of the disease being highest among nulliparous women and declining by 70% among those with three or more live births. Independent of nulliparity, a three-fold to five-fold excess risk among women who have had medical consultation for infertility is consistently found. The consistent finding of a 30% to 40% reduced risk associated with a prior tubal ligation or hysterectomy has been hypothetically attributed to the compromised ovarian function resulting from reduced blood flow. Few other risk factors reflecting endogenous hormonal status have been identified for ovarian cancer, and none with any consistency among studies.

HORMONE-REPLACEMENT THERAPY AND OVARIAN CANCER

HRT, primarily with estrogens, has been studied in various case-control and follow-up studies over the last 15 years. Most studies have found no consistent association between menopausal estrogen use and the risk of ovarian cancer. The overall relative risks in these studies have been close to 1.0 and yielded no evidence of higher risks for longer duration or higher dosages of estrogen. One investigation[55] found an increased risk of ovarian cancer among women who received both conjugated estrogens and DES for the treatment of menopausal symptoms. The number of cases in this study was limited, however, and the finding has not been confirmed.

ORAL CONTRACEPTIVES AND OVARIAN CANCER

Oral contraceptive use, by contrast, appears to exert a *marked protective effect*. The effect seems to be related to duration, with those using oral contraceptives for >5 years having an ~50% to 70% reduced risk of the disease.[56]

The encouraging nature of this result has overshadowed some inconsistencies among individual studies. Whether these differences reflect chance biases in some studies, the influences of varying patterns of use between studies, or meaningful biologic interactions remains unclear. Critical comparisons of the existing studies and new data may enhance the understanding of ovarian carcinogenesis and clarify risk-benefit issues, particularly as demographic patterns of oral contraceptive use continue to change. In particular, the influence of cessation of use on risk for ovarian cancer merits more study.

INFERTILITY TREATMENT

A history of drug therapy for infertility has been linked to increased ovarian cancer risk.[56,57] Generally, the lack of

testosterone; this may provide insights into the role of these hormones in prostate cancer etiology.

LIVER CANCER AND SEX STEROIDS

Hormones have been linked to liver tumors in men and women. The androgenic-anabolic steroids and oral contraceptives have been implicated.

ANDROGENIC-ANABOLIC STEROIDS AND LIVER CANCER

Androgenic-anabolic steroids in the form of oxymetholone or methyltestosterone derivatives were first linked to hepatocellular carcinoma by case reports[72] of patients undergoing long-term therapy for aplastic anemia. Patients with Fanconi anemia seemed to be at special risk, consistent with their heritable predisposition to acute leukemia and other cancers.[73] Liver tumors also have occurred when the steroids were used to treat conditions other than aplastic anemia, and some tumors have regressed on drug withdrawal. Although these findings are provocative, they are difficult to interpret because other risk factors for primary liver cancer, particularly the presence of hepatitis B virus, have not been evaluated in these studies, and these factors may be more common in these conditions. Resolution of these methodologic concerns was not important until the abuse of these androgenic drugs by body builders and other athletes became common (see Chap. 119).

ORAL CONTRACEPTIVES AND BENIGN LIVER TUMORS

A number of clinical reports[74] describing the development of benign liver tumors in young women receiving oral contraceptives have appeared in the literature. These tumors were highly vascular and often presented as emergencies with abdominal hemorrhage and shock. Two analytic case-control studies[75,76] have linked these tumors to the use of oral contraceptives. The risk for users of 3 to 5 years was ~100 times that of nonusers, and the risk for users of 7 years or more was ~500 times that of nonusers. The risks also appear to be higher for users older than 30 years of age and for users of relatively high potency pills. Although the relative risk is high, the absolute risk is not large for this rare tumor. The risk of hepatocellular adenoma among women younger than 30 years of age may be no more than 3 in 100,000 contraceptive users per year. Over this age, the absolute risk probably is greater but has not been precisely estimated. A study concluded that these high relative risks are more likely related to the high-dose preparations used in the early years of oral contraception and that current dosage regimens are associated with substantially smaller increases in risk.[77]

ORAL CONTRACEPTIVES AND LIVER CANCER

Because of the findings of these benign tumors and the role of the liver in metabolizing steroid hormones, much concern has been expressed over the potential for a relationship between oral contraceptive use and the risk of malignant liver tumors. Thus, the reports of a duration-related excess risk of this tumor with oral contraceptive use from six case-control investigations in the 1980s was further cause for substantial concern. The overall excesses were around 2.5-fold for women who had "ever used" oral contraceptives and more than nine-fold for long-term users.[78] All of these reports were from countries with low incidence rates of primary liver cancer and the number of cases in each study was limited, ranging from 12 to 26 patients. A study[79] in the United States that included 76 women who died of this tumor has confirmed these excess risks. Two investigations[80,81] conducted in high-risk countries have not noted an excess risk with contraceptive use, but in each instance the numbers of long-term users was few.

OTHER TUMORS

For some time, the speculation has been that endogenous hormones, particularly estrogens, might figure in the etiology of *malignant melanoma.* One follow-up study and one case-control study[82,83] conducted in the late 1970s implied that oral contraceptive users may be at 50% to 80% increased risk for this tumor. Partially because of the marked rise in incidence of malignant melanoma during the 1960s and 1970s, this finding caused considerable concern. Critical reviews noted the equally impressive rise in the incidence of skin melanoma among men and pointed out that the two positive studies had not obtained information on other possible risk factors that might be related to oral contraceptive use, particularly the duration of exposure to sunlight. Several investigations were launched to assess this issue. Although the results have been mixed, the level of concern has declined.

Also, in the late 1970s, reports were published of a number of clinical series of cases of pituitary adenoma among young women, a high proportion of whom had recently stopped using oral contraceptives. Subsequent investigations[84] have indicated that this association probably was not causal but reflected the increased use of computed tomography in detection of pituitary abnormalities among women with postcontraceptive menstrual disorders.

A number of other tumors have been suggested to be related to sex hormone levels because of a higher incidence among women than among men, a relationship to reproductive characteristics, or isolated observations of altered frequency among exogenous hormone users. In this category are cancers of the *gallbladder, thyroid, kidney, colon,* and *lung.* Most of the observations concerning cancers at these sites remain preliminary and speculative, but they clearly mark these tumors as candidates for more analytical assessments in the future.

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